RESPONSE

I. Status of the Claims

No claims have been cancelled. No claims have been amended. No new claims have been added. Claims 5-7 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**.

II. Rejection of Claims 5-7 Under 35 U.S.C. § 101

The Action first rejects claims 5-7 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

The present application describes a novel G-protein coupled receptor (GPCR). However, the Action once again questions prediction of protein function based upon protein homology, citing the same articles cited in the First Office Action in this case, which was mailed on July 30, 2002 ("the First Action"), specifically, Bork and Koonin (1998, Nature Genetics *18*:313-318; "Bork and Koonin"), Ji *et al.* (1998, J. Biol. Chem. *273*:17299-17302; "Ji") and Yan *et al.* (2000, Science *290*:523-527; "Yan"). Unfortunately, and improperly, the Examiner does not even address Applicants remarks concerning the shortcomings of these articles as set forth in the response filed on December 2, 2002 ("the previous response"), to the First Action. Therefore, Applicants will again set forth the shortcomings of these articles, and point out the failure of these articles to support the alleged lack of utility of the presently claimed sequence.

First, with regard to the Bork and Koonin article, Bork and Koonin themselves conclude "(i)n summary, the currently available methods for sequence analysis are sophisticated, and while further improvements will certainly ensue, they are already capable of extracting subtle but functionally relevant signals from protein sequences (Bork and Koonin, page 317). Thus, the Bork and Koonin article is hardly indicative of a high level of uncertainty in assigning function based on sequence, and thus does not support the alleged lack of utility.

With regard to Ji, an exact quote from Ji completely undermines the question of asserted utility

based upon protein homology: "a substantial degree of amino acid homology is found between members of a particular subfamily, but comparisons between subfamilies show significantly less or no similarity" (Ji at 17299, first paragraph, emphasis added). This quote suggests that homology with members of a G-protein coupled receptor is indicative that the particular sequence is in fact a member of that subfamily - the fact that there is little or no homology between subfamilies is completely irrelevant. Thus, Ji does not support the alleged lack of utility.

Furthermore, regarding Yan, this paper cites only one example, two isoforms of the anhidrotic ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2). However, while it is true that this amino acid change results in binding to different receptors, it is important to note that the different receptors bound by the two isoforms are in fact related (Yan at page 523). Furthermore, the EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based solely on sequence similarity (Yan at page 523). Thus, Yan does not suggest a high level of uncertainty in assigning function based on sequence, and thus also does not support the alleged lack of utility.

The Action again states that "significant further research" (Action at page 5) is needed to practice the claimed invention. Applicants pointed out in the previous response that, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), which clearly states that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Furthermore, Applicants point out that significant commercial exploitation of nucleic acid sequences requires no more information than the nucleic acid sequence itself. Applications ranging from gene expression analysis or profiling (see below) to chromosomal mapping (see below) are practiced utilizing nucleic acid sequences and techniques that are well-known to those of skill in the art. The widespread commercial exploitation of nucleic acid sequence information points to the level of skill in the art, and thus directly contradicts the Examiner's allegation that "significant further research" is required to practice the claimed invention.

The Action also questions the applicability of the case law cited by Applicants in the previous response, stating that "the Response cites a device case law" and "(t)hus, applicants' argument citing a case law regarding a device is irrelevant to the instant case" (Action bridging pages 4 and 5). Section 101 of the Patent Act of 1952, 35 U.S.C. § 101, provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," may obtain a patent on the invention or discovery. Applicants point out that 35 U.S.C. § 101 covers devices (machine) as well as compositions, and makes no distinction between the two with regard to meeting the burden of complying with 35 U.S.C. § 101. Furthermore, the case law in question (*Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999)) cites *Brenner v. Manson*, 383 U.S. 519, 534 (1966), which the Examiner obviously believes is not "irrelevant to the instant case", since the Examiner himself cites this exact case three times in the Action (see Action at pages 4, 5 and 6). Additionally, other cases cited by Applicants in the previous response (*Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985) and *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)) do not concern devices, but rather compositions. Thus, this argument completely fails to support the alleged lack of utility of the presently claimed compositions.

Rather, with regard to the utility of the presently claimed sequence, as 60% of the pharmaceutical products currently being market by the entire industry target G-protein coupled receptors (Gurrath, 2001, Curr. Med. Chem. *8*:1605-1648), a preponderance of the evidence clearly weighs in favor of Applicants' assertion that the skilled artisan would readily recognize that the presently described sequences have a specific (the claimed GPCR proteins are encoded by a specific locus on the human genome), credible, and

well-established utility, for example in tracking gene expression. As set forth in the specification as originally filed, at least at page 6, lines 15-17, the claimed polynucleotide sequences can be used to track the expression of the gene encoding the described protein. In particular, the specification describes how the described sequence can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. As the present sequences are specific markers of the human genome (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, two such companies (Agilent acquired by American Home Products and Rosetta acquired by Merck) were viewed to have such "real world" value that they were acquired by large pharmaceutical companies for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been

widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotide, as described in the specification as originally filed, at least at page 3, line 8, the present nucleotide sequence has a specific utility in mapping a unique gene to a particular chromosome. This is evidenced by the fact that SEQ ID NO:1 can be used to map the presently claimed sequence to chromosome 1 (present within the chromosome 1 clone, Genbank Accession Number AC114490; alignment and the first page from the Genbank report are presented in **Exhibit B**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 1 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Applicants respectfully remind the Examiner that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence, as described above. Applicants respectfully submit that the practical scientific value of biologically validated, expressed and polyadenylated mRNA sequences is readily apparent to those

skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp..1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. The PTO has issued numerous patents on polynucleotide sequences that have not been directly shown to be associated "with any disease or condition", the condition apparently set forth by the Examiner as allegedly necessary to comply with 35 U.S.C. § 101. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,2812 (each of which claims short polynucleotide fragments), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring in the present Action. Additionally, the Office has recently issued U.S. Patent 6,043,052, which concerns an "orphan" G-Protein coupled receptor identified based only on homology to the orphan receptor GPR25, similar to the situation with Applicants' currently claimed sequence. Importantly, this issued patent also contains no examples of the "real world" utilities seemingly required in the present case. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section III, below), Applicants submit that the presently claimed polynucleotide must also meet the requirements of 35 U.S.C. § 101. Holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, as well as the reasons set forth in Applicants' response filed on December 2, 2002 to the First Office Action mailed on July 30, 2002, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-

established utility, the rejection of claims 5-7 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

III. Rejection of Claims 5-7 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 5-7 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 5-7 have been shown to have "a specific, substantial, and credible utility", as detailed in section II above, the present rejection of claims 5-7 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 5-7 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Li have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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